REMARKS

Reconsideration of the present application in view of the following remarks is respectively requested. Claims 1-7, 9-13, and 16-24 are pending.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-7, 9 and 16-24 stand under 35 U.S.C. §103(a) as allegedly unpatentable over the LEUKINE® Sargramostim product insert, in view of U.S. Patent No. 5,217,954 (Foster *et al.*) and U.S. Patent No. 6,620,784 (Ferrara *et al.*) and in the case of claims 4-7, further in view of U.S. Patent No. 5,545,536 (Kaushansky *et al.*). More specifically, it is asserted that (1) the Leukine patient insert teaches that sargramostim is provided in liquid form at a concentration of 500 mcg/mL, with 1.1% benzyl alcohol, 40 mg/mL mannitol, 10 mg/mL sucrose, and 1.2 mg/mL tromethamine, and contains warning that preparations containing benzyl alcohol should not be used in neonates; (2) Ferrara *et al.* teach the use of both benzyl alcohol and EDTA in therapeutic compositions VEGF-E, another cytokine, and state that EDTA is a chelating agent and that benzyl alcohol is a known antimicrobial agent; (3) Foster *et al.* teach the use of EDTA as a chelating agent for the stabilization of bFGF, also cytokine and state that the EDTA "stabilizes this protein against oxidation of its free cysteine residues or metal-induced aggregation, thereby preserving the homogeneity of the purified product;" and (4) the use of TRIS as a buffering agent in protein and pharmaceutical preparations is notoriously old and well known in the art. It is concluded that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the sargramostim preparation disclosed in the LEUKINE® insert by the addition of EDTA as taught by both Ferrara *et al.* and Foster *et al.* It is asserted that one of ordinary skill in the art would have been motivated to make the addition in order to prevent oxidation of the GM-CSF protein and in view of the recognition in the art that EDTA is generally useful for stabilizing compositions comprising cytokines, as evidenced by Ferrara *et al.* and Foster *et al.*

Applicants respectfully traverse this ground of rejection. Applicants submit that a *prima facie* case of obviousness has not been established by the Action: There is no sufficient

motivation for one of ordinary skill in the art to use EDTA to stabilize GM-CSF. First, Applicants disagree that the assertion in the Action that the Ferrara *et al.* reference and the Foster *et al.* reference in combination indicate that EDTA is generally useful for stabilizing compositions comprising cytokines. The term "cytokine," as known in the art, refers to extracellular signal protein or peptide that acts as a local mediator in cell-cell communication and encompasses a diverse group of proteins and peptides with different amino acid sequences and functions (*see*, *Molecular Biology of The Cell*, 4th Ed. Alberts *et al.*, ed., Garland Science, 2002, p. G:10, copy submitted with the Amendment dated January 29, 2004; Janeway *et al.*, *ImmunoBiology: The Immune System in Health and Disease*, 4th Ed., Current Biology Publications, 1999, pages 588-591, 597 and 598, copy enclosed). Because the above-noted references only relate to two cytokines (*i.e.*, VEGF-E and bFGF), the assertion in the Action that EDTA is generally useful for stabilizing compositions comprising cytokines is an unduly broad generalization. As such, it does not provide the requisite motivation for a proper obviousness rejection.

Applicants further submit that there is no sufficient disclosure in the Ferrara *et al.* reference even to support that EDTA is actually effective in stabilizing VEGF-E. This reference is primarily related to the identification of VEGF-E and its uses: EDTA is only listed as a chelating agent with many other carriers, excipients or stabilizers. In addition, no experimental data showing that EDTA stabilizes VEGF-E is provided. Applicants submit that one of ordinary skill in the art would not have known from this reference that EDTA stabilizes VEGF-E.

Even assuming for the sake of argument that the Ferrara *et al.* discloses that EDTA is effective in stabilizing VEGF-E, Applicants submit that one skilled in the art would not have known that EDTA stabilizes GM-CSF. VEGF-E is both structurally and functionally different from GM-CSF. VEGF-E and GM-CSF only have about 15% sequence identity. In addition, GM-CSF stimulates the proliferation and differentiation of various hematopoietic progenitor cells in myeloid lineage and also activates or enhances many of the functional activities of mature neutrophils, monocytes, dendritic cells and macrophages (*see*, page 1, lines 6-11 of the present application), whereas VEGF-E stimulates the release of tissue factor, the proliferation, chemotaxis and sprouting of cultured vascular endothelial cells *in vitro* and

angiogenesis *in vivo* (*see*, http://www.copewithcytokines.de/cope.cgi?010014, downloaded on May 13, 2005, copy enclosed). In view of the structural and functional differences, one skilled in the art, even assuming that EDTA can stabilize VEGF-E, would not have known that EDTA is effective in stabilizing GM-CSF. Additional support for the above statement may be found in the enclosed review article of Wang (Instability, Stabilization, and Formulation of Liquid Protein Pharmaceuticals, *International Journal of Pharmaceutics* 185: 129-88, 1999, discussed in more detail below), which indicates that proteins have to be evaluated individually to develop stable liquid formulations.

Similarly, Applicants submit that the Foster *et al.* reference also fails to provide the necessary motivation for using EDTA to stabilize GM-CSF. That both bFGF and GM-CSF are cytokines is insufficient for motivating one of ordinary skill in the art to stabilize GM-CSF with EDTA. bFGF and GM-CSF differ from each other both structurally and functionally. They only share about 10% sequence identity. In addition, bFGF is known as a potent mitogen for a wide variety of cell types of mesodermal and neuroectodermal origin (*see*, column 6, lines 13-44 of the Foster *et al.* reference), whereas as indicated above, GM-CSF stimulates the proliferation and differentiation of various hematopoietic progenitor cells in myeloid lineage and also activates or enhances many of the functional activities of mature neutrophils, monocytes, dendritic cells and macrophages. Accordingly, Applicants submit that in view of the sequence and functional differences between bFGF and GM-CSF, one skilled in the art would not have been motivated to use EDTA to stabilize GM-CSF based on the use of EDTA in stabilizing bFGF. Furthermore, as identified in the Action, the Foster reference states that EDTA "stabilizes this protein against oxidation of its free cysteine residues or metal-induced aggregation, thereby preserving the homogeneity of the purifed product." This reference also indicates that it is likely that metals destabilize bFGF-containing solutions by catalyzing auto-oxidation of free cysteines in bFGF (*see*, column 1, lines 23-26, column 7, line 50 to column 8, line 41 of the Foster *et al.* reference). However, unlike bFGF, GM-CSF does not contain any free cysteines. The four cysteine residues in GM-CSF form two disulfide bridges (*see*, Shanafelt and Kastelein, *Proc. Natl. Acad. Sci. USA 86*: 4872-6, 1989, copy enclosed). Accordingly, one of ordinary skill in the art would not have used EDTA to stabilize GM-CSF in view of the Foster *et al.* reference.

Additional support for the lack of motivation to combine the cited references may also be found in the Wang reference, indicating that proteins have to be evaluated individually to develop stable liquid formulations.

Moreover, even assuming for the sake of argument that there was sufficient motivation for combining the cited references, Applicants submit that there would not be reasonable likelihood for one skilled in the art to be successful in using EDTA in stabilizing GM-CSF. As indicated in the Wang reference, it is unpredictable whether a particular protein is stable under given conditions. This article states that "the structural differences among different proteins are so significant that generalization of universal stabilization strategies has not been successful" and "[u]nfortunartely, there is no single pathway to follow in formulating" a liquid protein pharmaceutical (*see*, the last paragraph of the right column at pages 130 and 178 of the Wang reference). Various intrinsic factors (*e.g.*, hydrophobic amino acid residues and their locations, hydrogen bonding, and secondary structure) and extrinsic factors (*e.g.*, temperature, formulation pH, adsorption, salts, metal ions, chelating agents, shaking and shearing, protein denaturants, non-aqueous solvents, protein concentration, protein source and purity, protein morphism, high pressure, other excipients including sugars and polyols, surfactants, polyethylene glycols, polymers, and amino acids) affect the stability of a protein (*see*, pages 137, 145-153, and 163-174 of the Wang reference). Thus, to stabilize a particular protein, one of ordinary skill in the art has to experiment with multiple factors. Even if it happens that such a person chooses to experiment with a chelating agent, that person would not have a reasonable likelihood of success in stabilizing a particular protein because "chelating agents such as EDTA and citric acid may destabilize a protein by binding to the protein and/or its critical metal ions" and because the effect of chelating agents is complex, depending on metal ions present in the protein formulation, oxidation mechanism and type and concentration of the chelating agent (*see*, section 3.3.6 at page 150 of the Wang reference). Accordingly, the combination of the references cited in the Office Action would at most suggest to one of ordinary skill in the art to try to use EDTA for stabilizing GM-CSF. However, obvious to try or to experiment is not sufficient for establishing an obviousness rejection (*see*, *Yamanouchi Pharmaceutical Co. Ltd. V. Marsam Pharmaceuticals, Inc.*, 231 F.3d 1339, 56 USPQ2d 1641 (Fed. Cir. 2000).

In view of the above remarks, Applicants submit that this ground of rejection under 35 U.S.C. § 103(a) has been overcome. Withdrawal of this rejection is respectfully requested.

Claims 10-13 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the LEUKINE® Sargramostim product insert, U.S. Patent No. 6,620,784, U.S. Patent No. 5,217,954 (Foster *et al.*), and further in view of U.S. Patent No. 6,500,418 B1 (Dieckgraefe *et al.*)

Applicants respectfully traverse this ground of rejection. As discussed above, the composition of claim 1 is not obvious in view of the LEUKINE® Sargramostim product insert, Foster *et al.* and Ferrar *et al.* for failing to provide the necessary motivation for using EDTA to stabilize GM-CSF. Such a deficiency has not been remedied by the Dieckgraefe *et al.* reference. More specifically, the Dieckgraefe *et al.* reference relates to the use of GM-CSF in treating inflammatory bowel disease. It does not suggest or teach the use of EDTA in stabilizing GM-CSF. Thus, Applicants submit that the methods of using the composition of claim 1, as recited in claims 10-13, would not be deemed obvious in light of the Dieckgraefe *et al.* reference.

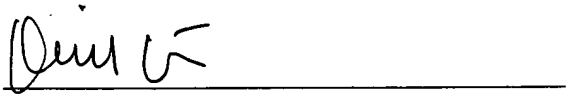
In view of the above remarks, Applicants submit that this ground of rejection under 35 U.S.C. § 103(a) has been overcome. Withdrawal of this rejection is respectfully requested.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants believe that all of the claims remaining in the application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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